Hybrid genetic networks: from Hoare logic to identification of parameters

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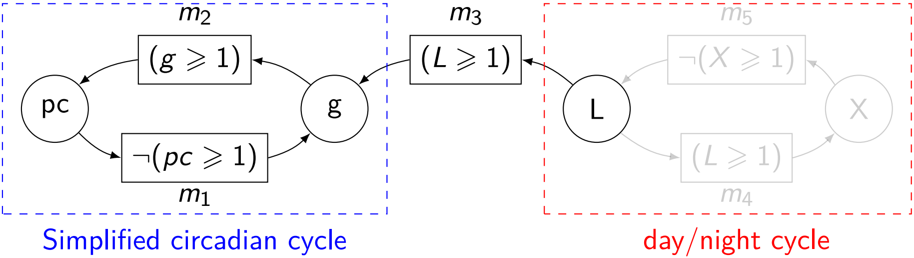
Objective - Identification of dynamic parameters



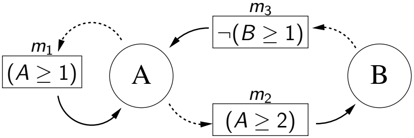
Legend :

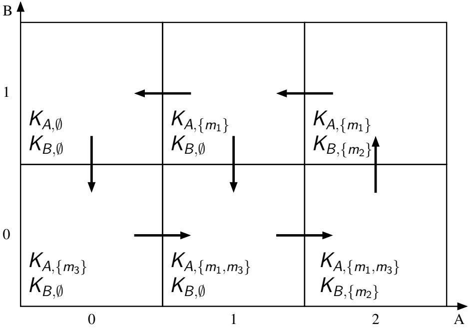
pc : **PER/CRY** protein complex inside the nucleus,

g : **per** and **cry** genes,

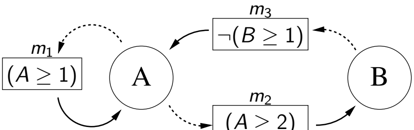
L : Light (Zeitgeber)

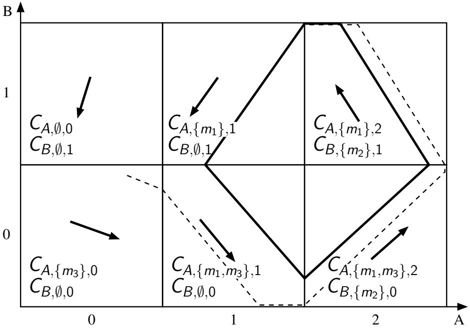
Stake : Identify dynamic parameters of genetic networks automatically.





- **Discrete** modelling framework.
- Space of homogeneous concentration.
- **Dynamic parameters** ex : $K_{A,\emptyset}$, $K_{A,\{m_3\}}$





- **Hybrid** modelling framework.
- Knowledge of time spent in each state of the system.
- **Celerities** ex : $C_{A,\emptyset,0}$, $C_{A,\emptyset,1}$, $C_{A,\emptyset,2}$

Hoare triple:

{Precondition}	(imperative program)	{Postcondition}
{P}	p	{Q}

- If P is satisfied before executing p, the postcondition Q will be satisfied after p.

Example: $\{x=0\} x := x + 1 \{x=1\}$

Hoare triple:

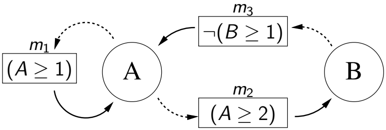
$$\color{red}{\{\text{Precondition}\}} \qquad \text{(imperative program)} \qquad \color{blue}{\{\text{Postcondition}\}}$$

$$\color{red}{\{\text{P}\}} \qquad \text{p} \qquad \color{blue}{\{\text{Q}\}}$$

- If P is satisfied before executing p, the postcondition Q will be satisfied after p.

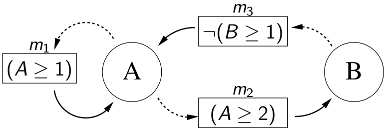
Example: $\color{red}{\{\text{x=0}\}}x := x + 1\color{blue}{\{\text{x=1}\}}$

- Biological paths can represent successions of events, similar to imperative programs



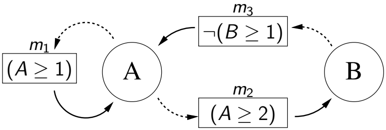
$$\left\{ \begin{array}{c} A = ? \\ B = ? \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
Final state: (2,0)				



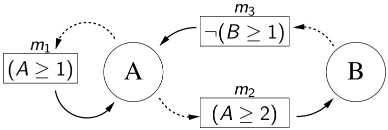
$$\left\{ \begin{array}{c} A = ? \\ B = ? \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(1,0)	A	$\omega 4$		
Final state: (2,0)				



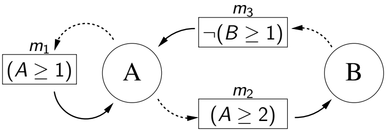
$$\left\{ \begin{array}{l} A = ? \\ B = ? \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	Parameters	ω	Resources	Constraints
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		
Final state: (2,0)				



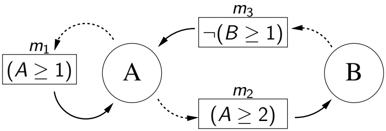
$$\left\{ \begin{array}{c} A = ? \\ B = ? \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,1)	A	$\omega 2$		
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		
Final state: (2,0)				



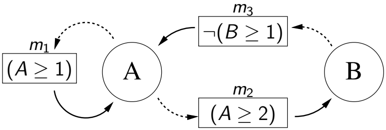
$$\left\{\begin{array}{l} A = 2 \\ B = 0 \end{array}\right\} B+; A-; B-; A+ \left\{\begin{array}{l} A = 2 \\ B = 0 \end{array}\right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$		
(2,1)	A	$\omega 2$		
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		
Final state: (2,0)				



$$\left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\}$$

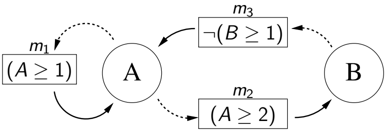
(A, B)	Parameters	ω	Resources	Constraints
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
(2,1)	A	$\omega 2$		
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		
Final state: (2,0)				



$$\left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\}$$

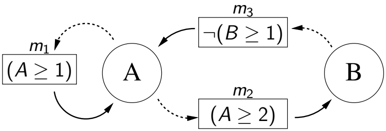
(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
(2,1)	A	$\omega 2$	m_1	$K_{A,\{m_1\}} < 2$
(1,1)	B	$\omega 3$		
(1,0)	A	$\omega 4$		
Final state: (2,0)				

Hoare logic - Use case : **Weakest Precondition**



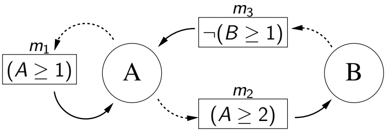
$$\left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
(2,1)	A	$\omega 2$	m_1	$K_{A,\{m_1\}} < 2$
(1,1)	B	$\omega 3$	$\emptyset$	$K_{A,\emptyset} < 1$
(1,0)	A	$\omega 4$		
Final state: (2,0)				



$$\left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{l} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
(2,1)	A	$\omega 2$	m_1	$K_{A,\{m_1\}} < 2$
(1,1)	B	$\omega 3$	$\emptyset$	$K_{A,\emptyset} < 1$
(1,0)	A	$\omega 4$	m_1, m_3	$K_{A,\{m_1,m_3\}} > 1$
Final state: (2,0)				

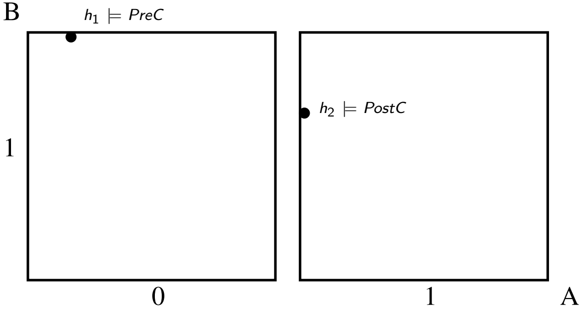


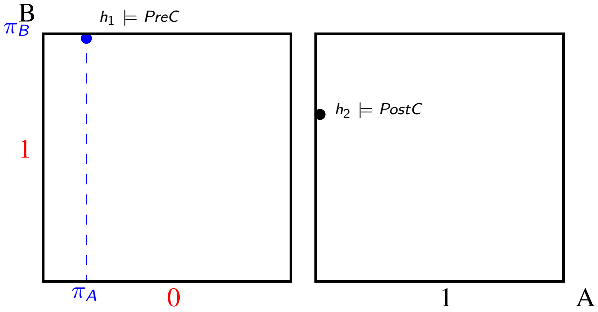
$$\left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\} B+; A-; B-; A+ \left\{ \begin{array}{c} A = 2 \\ B = 0 \end{array} \right\}$$

(A, B)	**Parameters**	ω	**Resources**	**Constraints**
(2,0)	B	$\omega 1$	m_2	$K_{B,\{m_2\}} > 0$
(2,1)	A	$\omega 2$	m_1	$K_{A,\{m_1\}} < 2$
(1,1)	B	$\omega 3$	$\emptyset$	$K_{A,\emptyset} < 1$
(1,0)	A	$\omega 4$	m_1, m_3	$K_{A,\{m_1,m_3\}} > 1$
Final state: (2,0)				

- **Modified Hoare logic** adapted to the hybrid modelling framework.

Modified Hoare logic - Semantics

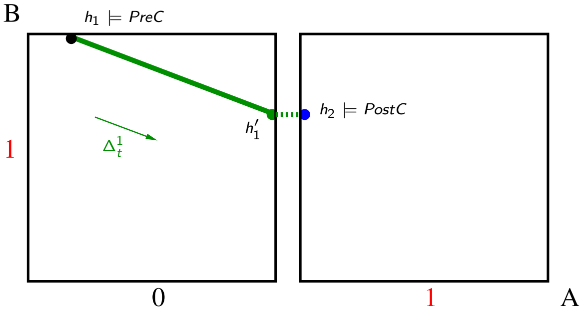




$$\left\{\begin{matrix} D \\ H \end{matrix}\right\}$$

Property language :

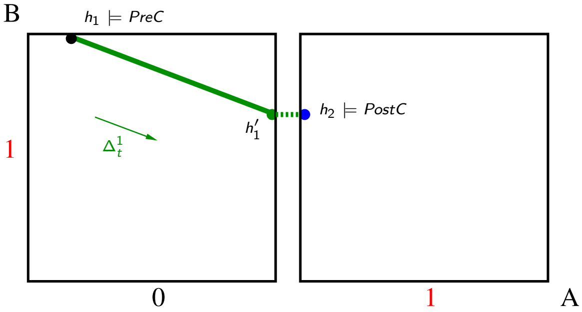
All couples **(D,H)** formed by a discrete and hybrid conditions.



$$\left\{\begin{matrix} D \\ H \end{matrix}\right\} \begin{pmatrix} \Delta_t^1 \\ \top \\ A+ \end{pmatrix}$$

Path language : Describe a biological behaviour p:

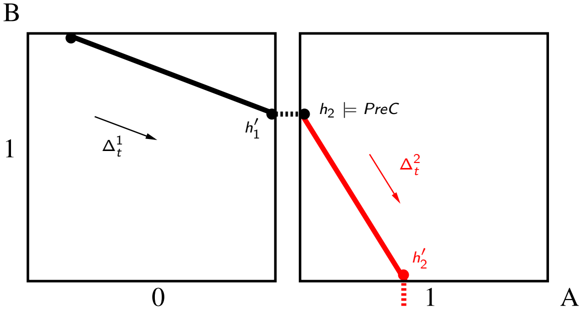
$$p :== \varepsilon \mid (\Delta t, a, v\pm) \mid p \; ; \; p$$



$$\left\{ \begin{array}{c} D \\ H \end{array} \right\} \begin{pmatrix} \Delta_t^1 \\ \top \\ A+ \end{pmatrix} \left\{ \begin{array}{c} D_1 \equiv (\eta_A = 1 \wedge \eta_B = 1) \\ H_1 \equiv (\pi_B = 0.67) \end{array} \right\}$$

Path language : Describe a biological behaviour p:

$$p :== \ \varepsilon \mid (\Delta t, a, v\pm) \mid p \ ; \ p$$



$$\begin{Bmatrix} D \\ H \end{Bmatrix} \begin{pmatrix} \Delta_t^1 \\ \top \\ A+ \end{pmatrix} ; \begin{pmatrix} \Delta_t^2 \\ \top \\ B- \end{pmatrix} \begin{Bmatrix} D_2 \\ H_2 \end{Bmatrix}$$

Path language : Describe a biological behaviour p:

$$p :== \ \varepsilon \mid (\Delta t, a, v\pm) \mid p \ ; \ p$$

$$\begin{Bmatrix} \color{red}{D} \\ \color{red}{H} \end{Bmatrix} \begin{pmatrix} T_1 \\ \top \\ A+ \end{pmatrix} \begin{Bmatrix} \color{blue}{D'} \\ \color{blue}{H'} \end{Bmatrix}$$

Objective : Determine conditions which make compatible the model with observed path.

$$\left\{\begin{matrix} D \\ H \end{matrix}\right\} \begin{pmatrix} T_1 \\ \top \\ A+ \end{pmatrix} \left\{\begin{matrix} D' \\ H' \end{matrix}\right\}$$

Objective : Determine conditions which make compatible the model with observed path.

Weakest Precondition: $\mathrm{WP}^i_f(p, Post) \equiv (D, H_{i,f})$

$$\left\{ \begin{array}{c} D \\ H \end{array} \right\} \varepsilon \left\{ \begin{array}{c} D' \\ H' \end{array} \right\}$$

Objective : Determine conditions which make compatible the model with observed path.
Weakest Precondition: $\mathrm{WP}^i_f(p, Post) \equiv (D, H_{i,f})$

- If $p = \varepsilon$, then $D \equiv D'$ and $H_{i,f} \equiv {H'}_f$;

$$\begin{Bmatrix} D \\ H \end{Bmatrix} \begin{pmatrix} T_1 \\ \top \\ A+ \end{pmatrix} \begin{Bmatrix} D' \\ H' \end{Bmatrix}$$

Objective : Determine conditions which make compatible the model with observed path.

Weakest Precondition: $\mathrm{WP}^i_f(p, Post) \equiv (D, H_{i,f})$

- If $p = \varepsilon$, then $D \equiv D'$ and $H_{i,f} \equiv H'_f$;
- If $p = (\Delta t, assert, v\pm)$:
  - $D \equiv D'[\eta_v \backslash \eta_v \pm 1]$,
  - $H_{i,f} \equiv H'_f \wedge \Phi^{\pm}_v(\Delta t) \wedge \neg \mathcal{W}^{\pm}_v \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$;

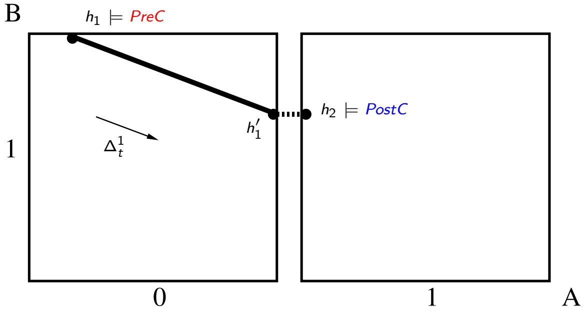
$$\begin{Bmatrix} D \\ H \end{Bmatrix} p_1; p_2 \begin{Bmatrix} D' \\ H' \end{Bmatrix}$$

Objective : Determine conditions which make compatible the model with observed path.

Weakest Precondition: $\mathrm{WP}^i_f(p, Post) \equiv (D, H_{i,f})$

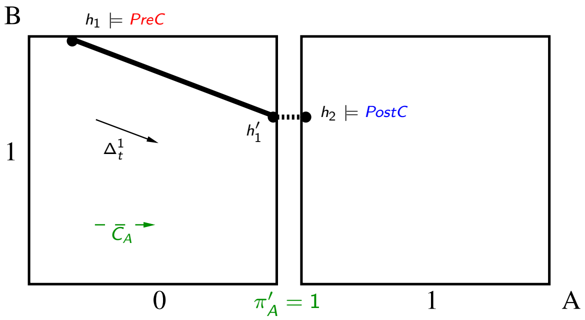
- If $p = \varepsilon$, then $D \equiv D'$ and $H_{i,f} \equiv H'_f$;
- If $p = (\Delta t, assert, v\pm)$:
  - $D \equiv D'[\eta_v \backslash \eta_v \pm 1]$,
  - $H_{i,f} \equiv H'_f \wedge \Phi^{\pm}_v(\Delta t) \wedge \neg \mathcal{W}^{\pm}_v \wedge \mathcal{F}_v(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_v$;
- If $p = p_1; p_2$:
  - $\mathrm{WP}^i_f(p_1; p_2, Post) \equiv \mathrm{WP}^i_m(p_1, \mathrm{WP}^m_f(p_2, Post))$

$$H_{i,f} \equiv H'_f \wedge \Phi^+_A(\Delta t) \wedge \neg \mathcal{W}^+_A \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta^1_t \\ slide^-(B) \\ A+ \end{pmatrix}$$

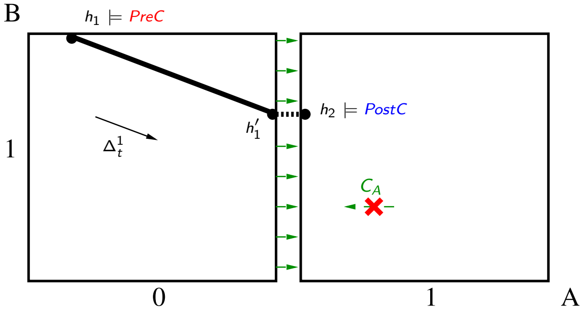
$$H_{i,f} \equiv H'_f \wedge \Phi_A^+(\Delta t) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta_t^1 \\ slide^-(B) \\ A+ \end{pmatrix}$$

$\Phi_A^+(\Delta_t^1)$: describes conditions where A increases its level expression.

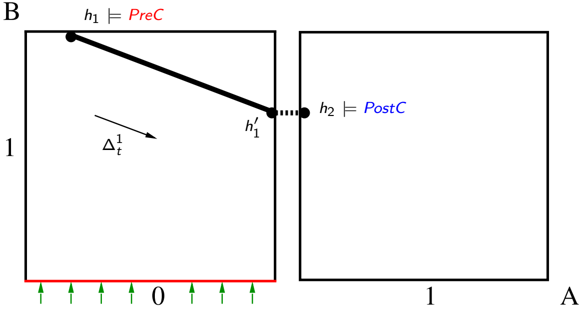
$$H_{i,f} \equiv H'_f \wedge \Phi_A^+(\Delta t) \wedge \neg\mathcal{W}_A^+ \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta_t^1 \\ slide^-(B) \\ A+ \end{pmatrix}$$

$\neg\mathcal{W}_A^+$: none internal or external wall for A.

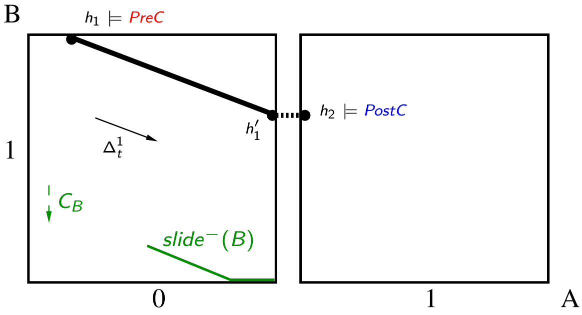
$$H_{i,f} \equiv H'_f \wedge \Phi_A^+(\Delta t) \wedge \neg \mathcal{W}_A^+ \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta_t^1 \\ slide^-(B) \\ A+ \end{pmatrix}$$

$\mathcal{F}_A(\Delta_t^1)$: A is the first component to change its qualitative state.

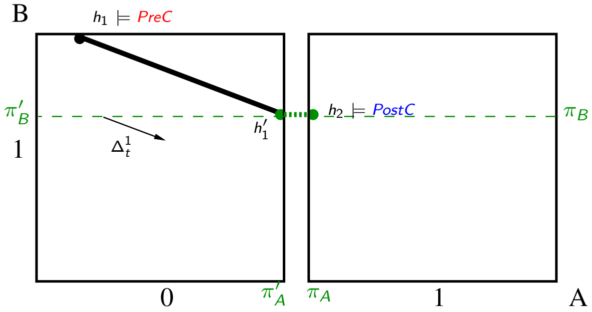
$$H_{i,f} \equiv H'_f \wedge \Phi^+_A(\Delta t) \wedge \neg \mathcal{W}^+_A \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta^1_t \\ slide^-(B) \\ A+ \end{pmatrix}$$

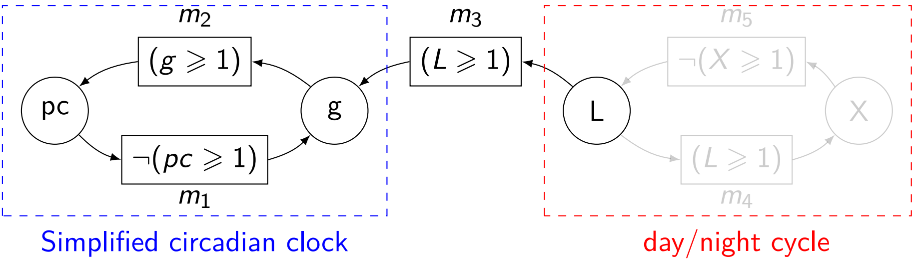
$\mathcal{A}(\Delta^1_t)$: translates assertion symbols in constraints.

$$H_{i,f} \equiv H'_f \wedge \Phi^+_A(\Delta t) \wedge \neg \mathcal{W}^+_A \wedge \mathcal{F}_A(\Delta t) \wedge \mathcal{A}(\Delta t) \wedge \mathcal{J}_A;$$



$$\begin{pmatrix} \Delta^1_t \\ slide^-(B) \\ A+ \end{pmatrix}$$

$\mathcal{J}_A$: makes the junction of positions between two successive states.



$$\left\{\begin{matrix} D_0 \\ H_0 \end{matrix}\right\} \begin{pmatrix} 0.9 \\ \top \\ pc- \end{pmatrix} ; \begin{pmatrix} 4.5 \\ \top \\ g+ \end{pmatrix} ; \begin{pmatrix} 0.6 \\ \top \\ X+ \end{pmatrix} ; \begin{pmatrix} 5.53 \\ \text{slide}^+(g) \\ pc+ \end{pmatrix} ; \begin{pmatrix} 0.47 \\ \top \\ L- \end{pmatrix} ; \begin{pmatrix} 5.4 \\ \text{slide}^+(pc) \\ g- \end{pmatrix} ; \begin{pmatrix} 0.6 \\ \text{slide}^-(L) \\ X- \end{pmatrix} ; \begin{pmatrix} 6 \\ \top \\ L+ \end{pmatrix} \left\{\begin{matrix} D_6 \\ H_6 \end{matrix}\right\}$$

$$D_6 \equiv (\eta_g = 0) \wedge (\eta_{pc} = 1) \wedge (\eta_L = 1) \wedge (\eta_X = 0)$$

$$H_6 \equiv (\pi_g = 0.12) \wedge (\pi_{pc} = 0.12) \wedge (\pi_L = 0) \wedge (\pi_X = 0)$$

Results of constraints for the simplified circadian clock :

$((((((((((\pi_g^{0\prime}=0.12) \wedge ((\pi_{pc}^{0}{}'=0.12) \wedge (\pi_L^{0\prime}=0))) \wedge (((\pi_L^1=1) \wedge ((C_{L,\{m5\},0}>0) \wedge (\pi_L^{1\prime}=(\pi_L^1-(C_{L,\{m5\},0}\times 6.6))))) \wedge$

$((\neg((C_{g,\emptyset,0}>0) \wedge (\pi_g^{1\prime}>(\pi_g^1-(C_{g,\emptyset,0}\times 6.6)))) \wedge (\neg((C_{pc,\emptyset,1}<0) \wedge (\pi_{pc}^{1}{}'<(\pi_{pc}^1-(C_{pc,\emptyset,1}\times 6.6)))) \wedge \neg((C_{X,\emptyset,0}>$

$0) \wedge (\pi_X^{1}{}'>(\pi_X^1-(C_{X,\emptyset,0}\times 6.6)))))) \wedge ((\pi_L^1=(1-\pi_L^{0\prime})) \wedge ((\pi_g^1=\pi_g^{0\prime}) \wedge ((\pi_{pc}^1=\pi_{pc}^{0}{}') \wedge (\pi_X^1=\pi_X^{0}{}'))))))) \wedge (((\pi_X^2=$

$0) \wedge ((C_{X,\emptyset,1}<0) \wedge (\pi_X^{2}{}'=(\pi_X^2-(C_{X,\emptyset,1}\times 0.6))))) \wedge ((\neg((C_{g,\emptyset,0}>0) \wedge (\pi_g^{2\prime}>(\pi_g^2-(C_{g,\emptyset,0}\times 0.6)))) \wedge (\neg((C_{pc,\emptyset,1}<$

$0) \wedge (\pi_{pc}^{2}{}'<(\pi_{pc}^2-(C_{pc,\emptyset,1}\times 0.6)))) \wedge \neg((C_{L,\emptyset,0}>0) \wedge (\pi_L^{2\prime}>(\pi_L^2-(C_{L,\emptyset,0}\times 0.6)))))) \wedge (((\pi_L^2=0) \wedge ((C_{L,\emptyset,0}<0) \Rightarrow$

$(\pi_L^{2\prime}<(\pi_L^2-(C_{L,\emptyset,0}\times 0.6))))) \wedge ((\pi_X^2=(1-\pi_X^{1}{}')) \wedge ((\pi_g^2=\pi_g^{1}{}') \wedge ((\pi_{pc}^2=\pi_{pc}^{1}{}') \wedge (\pi_L^2=\pi_L^{1\prime}))))))) \wedge (((\pi_g^3=0) \wedge ((C_{g,\emptyset,1}<$

$0) \wedge (\pi_g^{3\prime}=(\pi_g^3-(C_{g,\emptyset,1}\times 5.4))))) \wedge ((\neg((C_{pc,\{m2\},1}<0) \wedge (\pi_{pc}^{3}{}'<(\pi_{pc}^3-(C_{pc,\{m2\},1}\times 5.4)))) \wedge (\neg((C_{L,\emptyset,0}>0) \wedge (\pi_L^{3\prime}>$

$(\pi_L^3-(C_{L,\emptyset,0}\times 5.4)))) \wedge \neg((C_{X,\emptyset,1}<0) \wedge (\pi_X^{3}{}'<(\pi_X^3-(C_{X,\emptyset,1}\times 5.4)))))) \wedge (((\pi_{pc}^3=1) \wedge ((C_{pc,\{m2\},1}>0) \Rightarrow (\pi_{pc}^{3}{}'>$

$(\pi_{pc}^3-(C_{pc,\{m2\},1}\times 5.4))))) \wedge ((\pi_g^3=(1-\pi_g^{2\prime})) \wedge ((\pi_{pc}^3=\pi_{pc}^{2}{}') \wedge ((\pi_L^3=\pi_L^{2\prime}) \wedge (\pi_X^3=\pi_X^{2}{}')))))))) \wedge (((\pi_L^4=0) \wedge ((C_{L,\emptyset,1}<$

$0) \wedge (\pi_L^{4\prime}=(\pi_L^4-(C_{L,\emptyset,1}\times 0.47))))) \wedge ((\neg((C_{g,\{m3\},1}<0) \wedge (\pi_g^{4\prime}<(\pi_g^4-(C_{g,\{m3\},1}\times 0.47)))) \wedge (\neg((C_{pc,\{m2\},1}<$

$0) \wedge (\pi_{pc}^{4}{}'<(\pi_{pc}^4-(C_{pc,\{m2\},1}\times 0.47)))) \wedge \neg((C_{X,\{m4\},1}<0) \wedge (\pi_X^{4}{}'<(\pi_X^4-(C_{X,\{m4\},1}\times 0.47)))))) \wedge ((\pi_L^4=$

$(1-\pi_L^{3\prime})) \wedge ((\pi_g^4=\pi_g^{3\prime}) \wedge ((\pi_{pc}^4=\pi_{pc}^{3}{}') \wedge (\pi_X^4=\pi_X^{3}{}'))))))) \wedge (((\pi_{pc}^5=1) \wedge ((C_{pc,\{m2\},0}>0) \wedge (\pi_{pc}^{5}{}'=$

$(\pi_{pc}^5-(C_{pc,\{m2\},0}\times 5.53))))) \wedge ((\neg((C_{g,\{m1,m3\},1}<0) \wedge (\pi_g^{5\prime}<(\pi_g^5-(C_{g,\{m1,m3\},1}\times 5.53)))) \wedge (\neg((C_{L,\emptyset,1}<0) \wedge (\pi_L^{5\prime}<$

$(\pi_L^5-(C_{L,\emptyset,1}\times 5.53)))) \wedge \neg((C_{X,\{m4\},1}<0) \wedge (\pi_X^{5}{}'<(\pi_X^5-(C_{X,\{m4\},1}\times 5.53)))))) \wedge (((\pi_g^5=1) \wedge ((C_{g,\{m1,m3\},1}>0) \Rightarrow$

$(\pi_g^{5\prime}>(\pi_g^5-(C_{g,\{m1,m3\},1}\times 5.53))))) \wedge ((\pi_{pc}^5=(1-\pi_{pc}^{4}{}')) \wedge ((\pi_g^5=\pi_g^{4\prime}) \wedge ((\pi_L^5=\pi_L^{4\prime}) \wedge (\pi_X^5=\pi_X^{4}{}')))))))) \wedge (((\pi_X^6=$

$1) \wedge ((C_{X,\{m4\},0}>0) \wedge (\pi_X^{6}{}'=(\pi_X^6-(C_{X,\{m4\},0}\times 0.6))))) \wedge ((\neg((C_{g,\{m1,m3\},1}<0) \wedge [\ldots]$

Conclusion

- program developped and constraints represented as **DNF**,
- Simplify on the fly :

$$FNC : \ldots \wedge \left[(C_{v,\omega,n} < 0) \vee (\ldots) \right] \wedge (C_{v,\omega,n} \geq 0) \wedge \ldots$$

$2^{27} \rightarrow 2^{5}$ disjunctive logical connectives in our example

- Constraints adapted for constraint solver (**ibex**)

- program developped and constraints represented as **DNF**,
- Simplify on the fly :

$$FNC : \ldots \wedge \left[(C_{v,\omega,n} < 0) \vee (\ldots) \right] \wedge (C_{v,\omega,n} \geq 0) \wedge \ldots$$

$2^{27} \rightarrow 2^{5}$ disjunctive logical connectives in our example

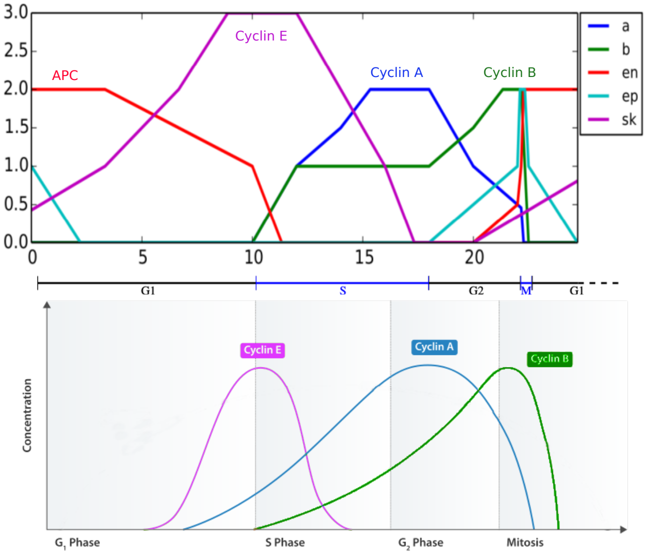
- Constraints adapted for constraint solver (**ibex**)

Perspective :

- Biological coupling between cell cycle and circadian clock

Thank you

Appendix - Result of cell cycle



$\Phi_A^+(T_1)$: describes conditions where A increases its level expression.

$$\Phi_A^+(\Delta t) \equiv ({\pi_A^i}' = 1) \quad \wedge \bigwedge_{\substack{\omega \subset R^-(A) \\ n \in [\![0, b_A]\!]}} \Big(\big(\Phi_A^\omega \wedge (\eta_A = n)\big) \Rightarrow (C_{A,\omega,n} > 0) \wedge (\pi_A^i = {\pi_A^i}' - C_{A,\omega,n} \cdot \Delta t) \Big)$$

$\Phi_A^+(T_1)$: describes conditions where A increases its level expression.

$$\Phi_A^+(\Delta t) \equiv ({\pi_A^i}' = 1) \quad \wedge \bigwedge_{\substack{\omega \subset R^-(A) \\ n \in [\![0, b_A]\!]}} \Big(\big(\Phi_A^\omega \wedge (\eta_A = n)\big) \Rightarrow (C_{A,\omega,n} > 0) \wedge (\pi_A^i = {\pi_A^i}' - C_{A,\omega,n} \cdot \Delta t) \Big)$$

$\neg\mathcal{W}_A^+$: none internal or external wall for A.

$$\mathcal{W}_A^+ \equiv \mathrm{IW}_A^+ \vee \mathrm{EW}_A^+$$

$$\mathrm{EW}_A^+ \equiv (\eta_A = b_A) \wedge \bigwedge_{\omega \subset R^-(A)} (\Phi_A^\omega \Rightarrow C_{A,\omega,b_A} > 0)$$

$$\mathrm{IW}_A^+ \equiv (\eta_A < b_A) \wedge \bigwedge_{\substack{\omega, \omega' \subset R^-(A) \\ n \in [\![0, b_A]\!]}} \Big(\big((\eta_A = n) \wedge (m = n+1) \wedge \Phi_A^\omega \wedge \Phi_{A+}^{\omega'}\big) \Rightarrow C_{A,\omega,n} > 0 \wedge C_{A,\omega',m} < 0 \Big)$$

$\mathcal{F}_A(T_1)$: A is the first component to change its qualitative state.

$$\mathcal{F}_A(\Delta t) \equiv \bigwedge_{u \in V \setminus \{A\}}$$

$$\Bigg(\bigwedge_{\substack{\omega \subset R^-(u) \\ n \in [\![0, b_u]\!]}} \big((\eta_u = n) \wedge \Phi_u^\omega \wedge C_{u,\omega,n} > 0 \wedge \pi_{u,i} > \pi'_{u,i} - C_{u,\omega,n} \cdot \Delta t \big) \Rightarrow \mathcal{W}_u^+ \Bigg)$$

$$\wedge \Bigg(\bigwedge_{\substack{\omega \subset R^-(u) \\ n \in [\![0, b_u]\!]}} \big((\eta_u = n) \wedge \Phi_u^\omega \wedge C_{u,\omega,n} < 0 \wedge \pi_{u,i} < \pi'_{u,i} - C_{u,\omega,n} \cdot \Delta t \big) \Rightarrow \mathcal{W}_u^- \Bigg)$$

$\mathcal{A}(T_1)$: translates assertion symbols in constraints.

$$\mathcal{A}(\Delta t, a) \equiv \bigwedge_{\substack{i \in [\![1,n]\!] \\ v_i \in V \\ \omega_i \in R^-(v_i) \\ n_i \in [\![0, b_{v_i}]\!]}} \left(\bigwedge_{i \in [\![1,n]\!]} \left((\eta_{v_i} = n_i) \wedge \Phi_{v_i}^{\omega_i} \right) \Rightarrow a \begin{bmatrix} C_{v_i} \backslash C_{v_i,\omega_{v_i},n_{v_i}} \\ \text{slide}(v_i) \backslash \mathcal{S}_{v_i,\omega_{v_i},n_i}(\Delta t) \\ \text{slide}^+(v_i) \backslash \mathcal{S}^+_{v_i,\omega_{v_i},n_i}(\Delta t) \\ \text{slide}^-(v_i) \backslash \mathcal{S}^-_{v_i,\omega_{v_i},n_i}(\Delta t) \end{bmatrix} \right.$$

$\mathcal{A}(T_1)$: translates assertion symbols in constraints.

$$\mathcal{A}(\Delta t, a) \equiv \bigwedge_{\substack{i \in [\![1,n]\!] \\ v_i \in V \\ \omega_i \in R^-(v_i) \\ n_i \in [\![0, b_{v_i}]\!]}} \left(\bigwedge_{i \in [\![1,n]\!]} \left((\eta_{v_i} = n_i) \wedge \Phi_{v_i}^{\omega_i} \right) \Rightarrow a \begin{bmatrix} C_{v_i} \setminus C_{v_i, \omega_{v_i}, n_{v_i}} \\ \text{slide}(v_i) \setminus \mathcal{S}_{v_i, \omega_{v_i}, n_i}(\Delta t) \\ \text{slide}^+(v_i) \setminus \mathcal{S}^+_{v_i, \omega_{v_i}, n_i}(\Delta t) \\ \text{slide}^-(v_i) \setminus \mathcal{S}^-_{v_i, \omega_{v_i}, n_i}(\Delta t) \end{bmatrix}$$

$\mathcal{J}_A$: makes the junction of positions between two successive states.

$$\mathcal{J}_A \equiv (\pi_A^f = 1 - {\pi_A^i}') \wedge \bigwedge_{u \in V \setminus \{A\}} (\pi_u^f = {\pi_u^i}') \ .$$